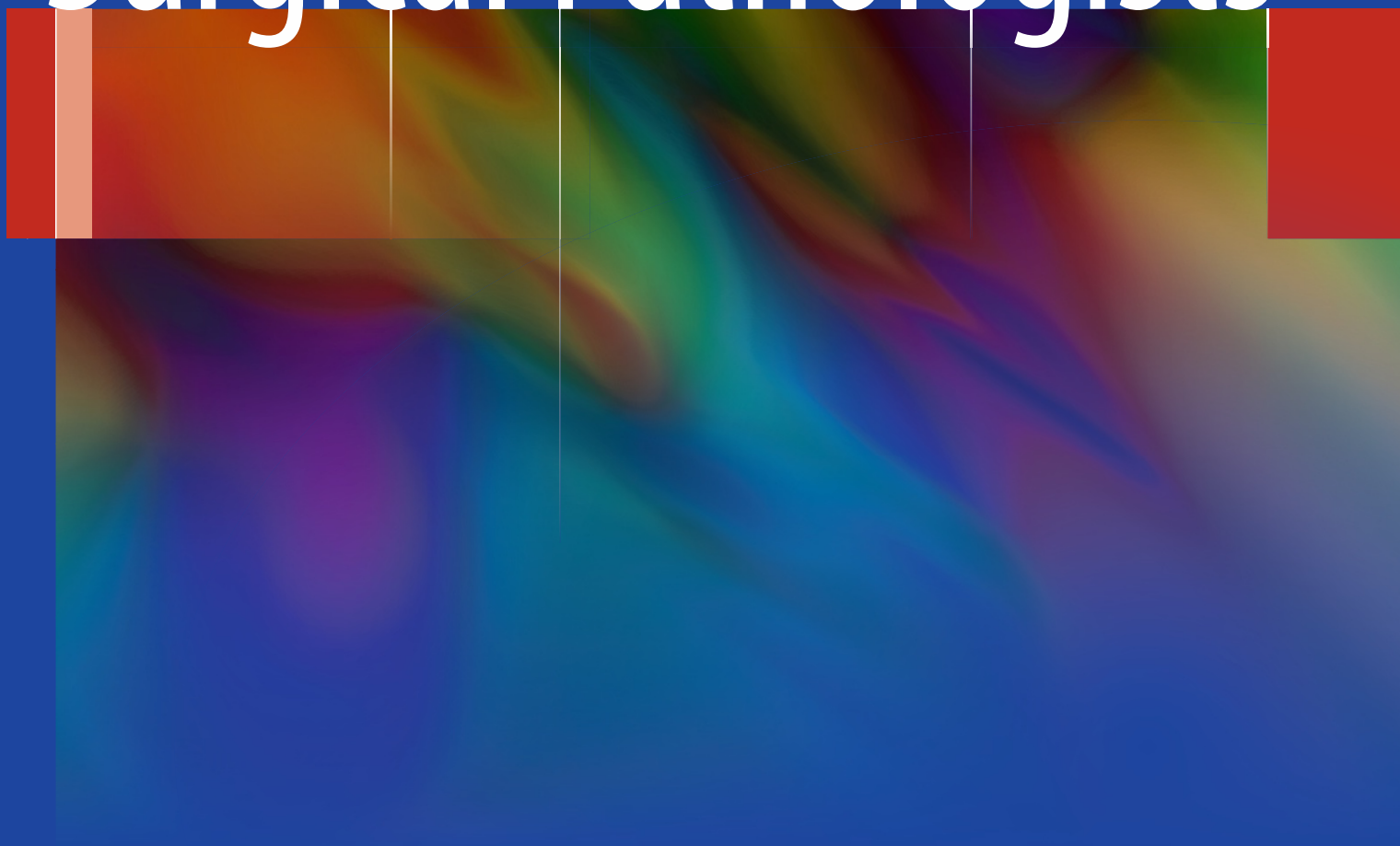
Natasha Rekhtman
Justin A. Bishop

Quick Reference Handbook for Surgical Pathologists



Springer

The Art of Writing a Pathology Report: What we Say … and What we Mean ☺ *by Natasha Rekhtman, Diana Molavi, and Justin Bishop*	
What we Say:	**What we Mean:**
This is a difficult case	I have no idea what this is
This lesion is difficult to classify	I am not familiar with the new WHO classification
Dr. X concurs with the diagnosis	Sure am glad somebody else here knows what this thing is
Case was shown at the quality assurance conference	We're all going down together
Invasion cannot be excluded	Probably invasive but don't feel like searching too hard … and it's time for my coffee break!
Lesion is best seen on permanent sections	We missed it on frozen
Stains are suboptimal	Did not work at all
Stains are non-contributory	Stained the wrong block
Stains are non-evaluable	Forgot to order
Tissue with cautery artifact	PLEASE … turn down that bovie!
Tumor approaches the margin	Positive margin but am going to dinner with the surgeon, so gotta be nice…
Tumor approaches the margin (#2)	Positive margin but am afraid of the surgeon
Representative sections submitted	One
Innumerable (as in polyps or mitotic figures)	More than 10
Rare (as in mitoses)	I didn't see any, but if I say zero there will be three on the first field when I show this case
No specific pathologic changes/ Non-diagnostic findings/ Mild chronic cholecystitis (gallbladder) / Chronic inflammation and lymphoid hyperplasia (tonsil)/ Reactive epithelial changes (esophagus)	Completely normal
Specimen did not survive processing	Was dropped on the floor and stepped on
Specimen was entirely submitted	Can't send me back to the bucket!
Possible lymph nodes	Hunks of fat
Recommend clinical correlation	Not my problem anymore!

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To Bob, Mark, Galina, and Katya.

Natasha Rekhtman

To Ashley, Riley, and Avery.

Justin Bishop

Preface

About this book

This book is a compilation of high-yield at-a-glance summaries for various topics frequently needed in a quick reference format at the microscope (or when cramming for the boards). As recently minted pathologists, we compiled this book from the perspective of pathologists-in-training and we gathered topics which we wanted to have in quick summary format during our recent residency and fellowships. Although written with the trainees in mind, the book may also be of interest to practicing pathologists as a practical quick reference by the microscope.

The book has a unique layout in that most of the information is presented in tables and diagrams accompanied by minimal explanatory text. Our motto for this book was to boil the information down to the essentials and key elements but with just enough commentary to be accessible to a newcomer to pathology. This book is not intended as a substitute for original resources or authoritative texts, but rather its purpose is to bring under one roof compact summaries for various types of information that trainees and practicing pathologists now search for in many different sources, and give the conceptual "lay of the land" with emphasis on "must know" facts. Certainly decisions about what constitutes "must know" and "high-yield" are highly subjective, and we apologize for any omissions which are inevitable by the nature of this book.

Our other main objective was to make the format of the book as user-friendly and easy to navigate as possible, such that one can quickly find the needed information. We thank our Springer editors for agreeing to publish this book in a non-standard format to help achieve this goal.

Contents

The focus is not organ-based morphologic criteria for which there are many excellent quick-summary resources, but rather the focus is everything else that helps a pathologist make a diagnosis (and pass the boards) with emphasis on the vast and fast-growing fields of immunohistochemistry (IHC) and molecular markers.

The book starts with unique introductory "primers" – at-a-glance 1-page summaries with diagrams on the main types of marker applications and high-yield facts (such as peculiar principles of cytokeratin designation). We highlighted the rules and biological principles behind various immunostains and special stains to help residents reason through a problem rather than having to resort to memorized panels. The other part of the IHC section contains a large compilation of general and organ-based applications of IHC with numerous immunopanels. This includes the classics (such as lung adenocarcinoma versus mesothelioma) and more recent applications (such as the work-up for mismatch repair proteins).

Other sections of the book contain various quick references that are often needed at the microscope but require frequent reminders. This includes a compilation of grading systems, common prognostic systems, and other criteria that are difficult to keep committed to memory (such as size cut-points for various micro-entities like thyroid papillary microcarcinoma). Also included are summaries for tumor syndromes with a particularly practical "slide-to-syndrome" summary where we highlighted which diagnoses or features should trigger consideration of a syndrome. In tumor genetics and cytogenetics we highlighted which tumors have unique molecular characteristics that can aid in the diagnosis or are used in prognostic/predictive testing.

Another high-yield section that is not usually covered in most pathology books is a compilation of quick clinical references geared for pathologists. This section contains resources that help pathologists interpret clinical information that may be highly informative in the differential diagnosis of tumors, including a primer on metastasis (what metastatic patterns are classic vs. exceptional for certain tumors) and serologic tumor markers. We also included a brief summary of targeted therapies for which pathologists may be asked to perform predictive marker testing.

Even though the focus of the book is not organ-based morphologic criteria, we included several sections with differentials that cut across all organs. For example, this section includes at-a-glance differentials for small round blue cell tumors, and classic differentials for certain morphologic features (such as which tumors are classically associated with granulomas or have staghorn vessels). We also included an illustrated guide to microorganisms. Finally, we compiled an illustrated glossary of histopathologic descriptors with illustrations of common objects these terms are said to resemble (such as storiform or palisaded, and what Orphan Annie's eyes actually look like!). Keep this by your side as you begin to tackle the large pathology books! We are also very excited to include a handy guide for pathology web resources by Terina Chen and a user-friendly CPT coding summary by Diana Molavi.

Sources

We used a variety of sources, including standard books and mountains of primary literature. However, most importantly our "world view" of pathology this early in our careers comes primarily from our outstanding teachers at The Johns Hopkins Hospital and Memorial Sloan-Kettering Cancer Center. From them we learned the approaches and principles that come only after years of experience but cannot be learned by reading books and papers. We were fortunate to learn pathology from these bril-

liant diagnosticians and generous educators, who shared their knowledge with us through sign outs, lectures and weekly unknowns during our residency at Johns Hopkins. We therefore can only take credit for organizing and presenting this stream of knowledge in a format easily accessible to a newcomer to pathology, and we give all credit for the many useful pearls and principles in this book to our teachers. On the other hand, we take full responsibility for any inaccuracies that may have inadvertently escaped our attention.

In conclusion
It is our hope that this book will be your best friend both at the microscope and in the late night hours of studying for the boards. Because the type of information covered in this book is rapidly evolving, please be sure to check the most current sources.

Natasha Rekhtman and Justin Bishop

How this book came about – part 1
I started working on this book in my second year of residency at The Johns Hopkins Hospital, although at that time I did not yet know that this was what I was doing. Like many pathologists, I am a very visual learner, and I firmly believe that a good table or diagram is worth many pages of text. Therefore I was desperately looking for resources that succinctly summarized the mountains of information I was trying to absorb, particularly in a format that was tabular or diagrammatic and was amenable to quick learning of the essentials. While there were many great resources for histologic criteria, what I felt was missing were quick references for the new and fast growing fields of immunostains and molecular markers, as well as other types of material frequently needed in pathologists' daily work but not available in a single source. I therefore started compiling these summaries and diagrams for my own use, and later started sharing them with my co-residents. After getting feedback that others were findings these summaries useful, and after I realized that creating them was an incredible motivator to learn and digest the information, I put together a small handbook which was generously printed by the Department of Pathology at Johns Hopkins as a Resident Manual in 2004 and 2007. Now in collaboration with Justin Bishop as my coeditor and main coauthor and with contributions from many former and current Hopkins residents and fellows and my current colleagues at Memorial Sloan-Kettering Cancer Center, this book has morphed into what it is today. Justin joined forces with me in the last two years, and I could not have dreamt of a more dedicated and talented collaborator, who made it possible to get this project completed.

Natasha Rekhtman

How this book came about – part 2
My first interaction with this book (universally known as the "Green Book" at Hopkins) was in 2006. The more senior residents had copies of a magical book that had all the answers I was seeking as a pathology intern. Desperate for something to boil down the massive amounts of information into one resource, my fellow first-year residents and I assembled crude bootleg copies of it. At the end of that year as she left Hopkins, Natasha distributed a new edition which remains a fixture at my microscope to this day. However, as the years passed and new waves of residents entered our program, original copies of the Green Book became increasingly scarce, and the quality of copies became increasingly poor as they became 2nd and 3rd generation. My chief resident year, I was frequently confronted with a question from the junior residents: "Where can I get a copy of that Green Book?" We had heard rumors about the possibility of it being published, but no one at Hopkins knew the status of the now-mythical Green Book. Intent on getting an answer, I contacted Natasha. As luck would have it, she needed a collaborator to push the project past the finish line, and that collaborator became me. Initially a great way to study for my boards, working on the book then became a means to stay on top of the newest information as I started signing out surgical pathology. Although perhaps it was a bigger commitment than I initially realized, it was well worth the effort, and I am extremely grateful to Natasha for allowing me to be a part of this very special project.

Justin Bishop

Acknowledgements

We were fortunate to learn pathology as residents and assistants in surgical pathology from the brilliant diagnosticians and dedicated educators of The Johns Hopkins surgical pathology team and other divisions. We are most grateful to all our teachers for sharing with us their knowledge and wisdom that serves as the foundation of this book.

We would like to sincerely thank all coauthors and reviewers for contributing their brainpower to this project with special thanks to Ashlie Burkart, Terina Chen, Amy Duffield, Diana Molavi and Janis Taube for lead-authoring various sections of this book. Very special thanks to Ashlie Burkart, Shien Michelli and Diana Molavi for reviewing various portions of this book, and penciling in multiple suggestions and question marks (as well as smiley faces…) and for being the constant source of encouragement over the years. We are most grateful to all Hopkins faculty and trainees for making suggestions/corrections and enthusiastic support over the years. This book would not be what it is today if it had not been vetted by several generations of keen Hopkins residents. We also want to thank our publishing team Gabriele Schroeder, Sandra Lesny, and Ellen Blasig at Springer and Patrick Waltemate at le-tex for all their efforts on behalf of this book.

Natasha also thanks her colleagues at Memorial Sloan-Kettering Cancer Center for their support and for generously sharing their knowledge and expertise.

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Table of Contents – At a Glance

Detailed Table of Contents

Unless otherwise specified, subsection authors are Justin Bishop and Natasha Rekhtman.

Abbreviations, Acronyms, and Designations

**See IHC index for alternative designations of antibodies/antigens

AFIP – Armed Forces Institute of Pathology
AJCC – American Joint Committee on Cancer
ALL – acute lymphoblastic leukemia/lymphoma
AML – acute myeloid leukemia
BAC – bronchioloalveolar carcinoma
Bx – biopsy
CA – carcinoma
CD – cluster of differentiation (as in CD3, CD20, etc.)
CHR – chromogranin
CIS – carcinoma in situ
CK – cytokeratin(s)
CLL/SLL – chronic lymphocytic leukemia/small lymphocytic lymphoma
CMV – cytomegalovirus
CNS – central nervous system
CRC – colorectal carcinoma
CT – computed tomography
Derm – dermatopathology
DNA – deoxyribonucleic acid
DDx – differential diagnosis
DLBCL – diffuse large B cell lymphoma
Dx – diagnosis
EBV – Epstein-Barr virus
EM – electron microscopy
ER – estrogen receptor
FL – follicular lymphoma
GI – gastrointestinal
GIST – gastrointestinal stromal tumor
GU – genitourinary
GYN – gynecologic
HCC – hepatocellular carcinoma
H&E – hematoxylin and eosin
H&N – head and neck
Heme – hematopathology
HHV8 – Human Herpesvirus 8
HMWCK – high molecular weight cytokeratins
HPF – high-power field (40X)
HPC – hemangiopericytoma
HPV – human papillomavirus
HSV – herpes simplex virus
HTLV – Human T-lymphotropic virus
ID – identification or identify
IHC – immunohistochemistry
IPMN – intraductal papillary mucinous neoplasm
ISH – in situ hybridization
JHH – Johns Hopkins Hospital
LMWCK – low molecular weight cytokeratins
LN – lymph node
MCL – mantle cell lymphoma
MCN – mucinous cystic neoplasm
MD – moderately differentiated
ME – myoepithelial
MEC – myoepithelial cells
Met – metastasis
MPNST – malignant peripheral nerve sheath tumor
MSKCC – Memorial Sloan-Kettering Cancer Center
MZL – marginal zone lymphoma
NE – neuroendocrine
NK – natural killer
NLPHL – nodular lymphocyte predominant Hodgkin Lymphoma
NOS – not otherwise specified
PCR – polymerase chain reaction
PD – poorly differentiated
PEComa – perivascular epithelioid cell tumor
PET – positron emission tomography
PNET – primitive neuroectodermal tumor
PR – progesterone receptor
PTC – papillary thyroid carcinoma
RBC – red blood cell
RCC – renal cell carcinoma
R-S cell – Reed Sternberg cell
Rx – therapy, treatment
SmCC – small cell carcinoma
SqCC – squamous cell carcinoma
SRBCT – small round blue cell tumor
SYN – synaptophysin
TB – tuberculosis
vs. – versus
WD – well differentiated
WHO – World Health Organization

Immunohistochemistry reactivity code

+++	Overexpressed or consistently diffuse
+	Positive
+/–	Usually positive
–/+	Usually negative
–	Negative

Chapter 1 Immunostains: Introduction

by Natasha Rekhtman and Justin Bishop

Applications of Immunohistochemistry (IHC) in Anatomic Pathology

(select examples)

1. **DIAGNOSIS OF TUMORS:**
   - **a. Classification of poorly differentiated neoplasms:**
     carcinoma (cytokeratin+) vs.
     lymphoma (CD45+) vs.
     melanoma (S100+, Melan-A+, HMB45+)
   - **b. Diagnosis of carcinoma of unknown primary:**
     colon (CDX2+) vs.
     lung (TTF-1+) vs.
     prostate (PSA+)
   - **c. Diagnosis of invasion:**
     loss of myoepithelial cells (breast cancer)
     loss of basal cells (prostate cancer)
     loss of basement membrane/collagen type IV (various carcinomas, rarely used)
2. **ASSESSMENT OF MARKERS REFLECTING PROGNOSIS ("PROGNOSTIC" MARKERS"):**
   Ki67/MIB1 (general proliferation marker)
   p53 (general marker of apoptosis)[1]
   HER2 (adverse prognosis in breast cancer)
   CD38 (adverse prognosis in chronic lymphocytic leukemia)
3. **ASSESSMENT OF MARKERS REFLECTING A THERAPEUTIC RESPONSE ("PREDICTIVE" OR "THERANOSTIC" MARKERS):**
   ER/PR (Tamoxifen for breast cancer)
   HER2 (Herceptin for breast cancer)
   c-kit (Gleevec for GIST, CML, other; mutations more predictive than IHC)
4. **DETECTION OF MICROMETASTASES:**
   melanoma (melanocytic markers)
   breast cancer (cytokeratins)
5. **IDENTIFICATION OF INFECTIOUS ORGANISMS[2]:**
   viruses (HSV, CMV)
   other organisms (Toxoplasma, Pneumocystis)

1. It may appear counterintuitive that p53, a well-known tumor-suppressor, is overexpressed in various tumors. This occurs because inactivating mutations in *p53* also disable protein degradation and lead to a robust p53 overexpression. In essence, robust overexpression of p53 is used as a surrogate marker for *p53* gene mutation.
2. Currently IHC is not widely used to identify bacteria and fungi (this is likely to change). These organisms are primarily evaluated by special stains (such as GMS), and some viruses may be identified by in situ hybridization (EBV, HPV).

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